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Evaluation of platelet parameters in patients with gestational diabetes mellitus (GDM)

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Abstract

Aim: Gestational diabetes mellitus (GDM) is the most common metabolic disease during pregnancy. In our study, we evaluated the role of platelet large cell ratio (PLCR) and immature granulocytes (%IG) in GDM.

Material and Method: Our study was conducted by retrospectively reviewing the records of 53 GDM patients between January 2019 and June 2020 at the clinics of Istanbul Training and Research Hospital. Thirty-eight healthy patients were included in the control group. GDM was diagnosed with 75g OGTT. The PLCR and IG% values obtained from the complete blood count of each patient performed in our hospital were studied.

Results: Gestational diabetes mellitus was detected in 53 of 91 patients included in the study. The mean age in the GDM group was higher than in the non-GDM (control) group (32.8±5.0 /26.9±5.0, p<0.001). There was no statistical difference between the groups in gestational week (GW), body mass index (BMI) and PLCR parameters. Both IG% and HbA1c values were statistically significantly higher in the GDM group than in the non-GDM group (0.6±0.2/0.5±0.1, p=0.002; 5.4±0.8/5.1±0.3, p=0.005, respectively). In the ROC curve analysis, the area under the curve (AUC) for the IG% value to predict the presence of GDM was 0.713 (0.606-0.821).

Discussion: This study investigated the values of PLCR and IG%, which are new inflammatory markers that have not been studied much, in GDM patients. We detected a statistically significant increase in IG% values in GDM patients and for the first time determined a cut-off value for this marker using ROC curve analysis.

Keywords

Gestational Diabetes Mellitus, Platelet Parameters, Immature Granulocyte

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Introduction

Gestational diabetes mellitus (GDM) is the most common metabolic disease in pregnancy [1] and is defined as carbohydrate intolerance first diagnosed during pregnancy [2,3]. It is estimated that 7% of all pregnancies are complicated by diabetes mellitus (DM), and 86% of these patients have GDM [2]. With the worldwide increase in obesity and sedentary lifestyle, the prevalence of DM is increasing [1]. The prevalence of GDM is also increasing with an increase in advanced-age pregnancies and obese patients [4]. Gestational diabetes mellitus affects both the mother and the fetus. It is associated with an increased risk of preeclampsia, premature rupture of membranes, dystocia, increased cesarean section rate, polyhydramnios, a large baby, and delayed fetal lung maturation [5]. In addition, women with GDM have an increased risk of developing type 2 DM later in life [1,2]. It is estimated that 50% of GDM patients will develop type 2 diabetes within 28 years after pregnancy [1].

Inflammatory markers have been observed at higher levels in GDM patients compared to normal pregnant women [6]. The development of GDM likely results from multiple factors that reduce insulin production by acting synergistically with the release of pro-inflammatory cytokines and impairment of pro-inflammatory signaling pathways [3]. Adiponectin, TNF-alpha, IL-6, alanine, branched-chain amino acids, adipocyte fatty acid-binding protein, and ferritin can be counted among the substances that have a high probability of influencing the development of GDM and will be used for GDM monitoring in the future [3]. It was pointed out that DM and, accordingly, GDM are associated with low-grade subchronic inflammation [7,8]. A complete blood count is a routinely ordered test at the initial evaluation of patients. It is well known that platelet parameters such as mean platelet volume (MPV), plateletcrit (PCT), platelet distribution width (PDW), which can be easily obtained from complete blood count, are associated with many inflammatory diseases and are used to monitor these diseases [4,9,10]. Supporting these data, changes in platelet parameters in GDM have been reported [11]. Platelet large cell ratio (PLCR) indicates the proportion of platelets larger than 12 fL. Normally, this proportion is 30% of the total platelet count. Large platelets are younger, contain more intracellular granules and, therefore have a greater thrombogenic potential [12]. It is ascertained that PLCR is mainly associated with MPV. This marker has also been found to be high in non-pregnant DM patients [10,13,14], but the situation in GDM patients remains uncertain.

The percentage of immature granulocytes (IG%) is an inflammatory marker seen in complete blood count. It has been reported that in inflammatory conditions, it rises much earlier than conventional parameters such as CRP [15,16]. Although some studies have found no association between GDM and %IG [17], there are still not enough studies on this topic. In our study, we aimed to elucidate the role of PLCR and %IG in GDM patients. Determining whether these inexpensive and easily obtained platelet parameters are valuable in the diagnosis of GDM patients is the main objective of our study.

Material and Methods

Our study was conducted by retrospectively reviewing the records of 53 patients diagnosed with GDM between January 2019 and June 2020 at the Obstetrics and Gynecology Outpatient Clinic of Istanbul Training and Research Hospital. The study patients were divided into two groups according to the presence of GDM diagnosis: the GDM group and the non-GDM group (healthy controls). Thirty-eight pregnant women who were monitored in our outpatient clinic, had no disease and a negative 75g oral glucose tolerance test (75g OGTT) were selected as a control group. GDM patients were then divided into two subgroups as insulin users and non-insulin users to compare relevant variables between them.

Gestational diabetes mellitus was diagnosed with 75g OGTT in accordance with the recommendation of IADPSG (International Association of Diabetes and Pregnancy Study Group). Patients were diagnosed with GDM if any of the fasting, first-hour and second-hour postload venous plasma glucose levels were equal to or higher than 92 mg/dL, 180 mg/dL and 153 mg/dL, respectively.

Patients diagnosed with pre-pregnancy DM, hypertension, renal disease, cardiovascular disease and neurological disease, and patients with a history of drug or substance use, the presence of infectious diseases, hematological diseases, immunological diseases and malignant diseases were excluded from the study. PLCR and IG% values obtained from the complete blood count of each patient performed in our hospital were studied. A complete blood count was performed with an automated hematology analyzer (XN 3000; Sysmex Corp., Kobe, Japan) from blood samples collected from taken from the patients' antecubital veins. Other patient outcomes were evaluated based on patient records.

Ethical approval for the study was obtained from the Ethics Committee of Istanbul Training and Research Hospital (Decision No: 2465, Date: 10/07/2020). Since our study was retrospective, written informed consent could not be obtained from the patients.

Statistical analysis

All statistical tests were performed using the Statistical Package program for Social Sciences 25.0 for Windows (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov or Shapiro-Wilk test was used to analyze the normality of the data. Normally distributed numerical data were expressed as mean ± SD, non-normally distributed parameters were expressed as median (25-75) percentiles, while categorical data were expressed as percentages. According to the data distribution, comparison of non-dependent numerical data was performed using Student's t-test and/or Mann-Whitney U test. Similarly, the relationship between parameters was evaluated with Pearson's or Spearman's correlation analysis according to the normality of the data. The IG% value was analyzed using univariate logistic regression analysis to predict the presence of GDM in patients. Figure 2 was constructed using the probability value obtained from the logistic regression analysis. The specificity and sensitivity of the IG% value best predicting GDM was calculated using ROC analysis. A p-value of <0.05 was accepted as statistical significance to be bidirectional.

Results

Gestational diabetes mellitus was detected in 53 of 91 patients

included in the study, and their clinical and demographic characteristics are shown in Table 1. When the mean age of the groups was compared, it was found that the mean age in the GDM group was higher than in the non-GDM (control) group (32.8±5.0 /26.9±5.0, p<0.001). There was no statistical difference between the groups in terms of gestational week (GW), body mass index (BMI) and PLCR parameters. Evaluation of IG% and HbA1c values revealed that both IG% and HbA1c values were statistically significantly higher in the GDM group than in the non-GDM group (0.6±0.2/0.5±0.1, p=0.002; 5.4±0.8/5.1±0.3, p=0.005, respectively) (Table 1).

Table 1. Comparison of demographic and laboratory characteristics of patients

Variables	GDM Group (n=53) Mean ± SD	Non-GDM Group (Healthy Controls) (n=38) Mean ±SD	p
Age (years)	32.8 ± 5.0	26.9 ± 5.0	<0.001
GW (weeks)	36.1 ± 2.7	36.5 ± 3.3	0.581
BMI (kg/m2)	31.0 ± 6.1	28.9 ± 4.4	0.086
Insulin dose (units/ml)	20 (10-34)	-	-
Insulin use, n (%)	22 (%41)	-	-
PLCR	31.8 ± 5.1	32.2 ± 7.7	0.799
IG%	0.6 ± 0.2	0.5 ± 0.1	0.002
HbA1c (%)	5.4 ± 0.8	5.1 ± 0.3	0.005

Values are described as Mean ± Standard Deviation, GW: Gestational week, BMI: Body mass index, PLCR: Platelet large cell ratio, IG%: The percentage of immature granulocytes

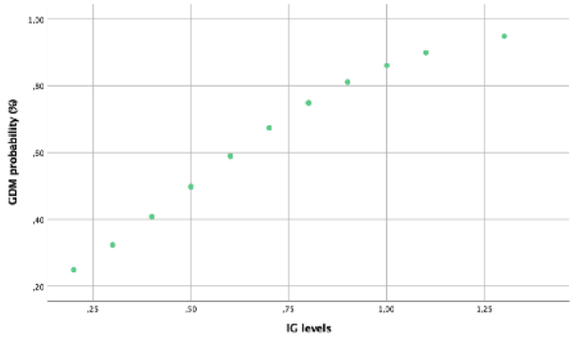

Figure 1. Graphical representation of the probability of pregnant women having GDM according to IG% values

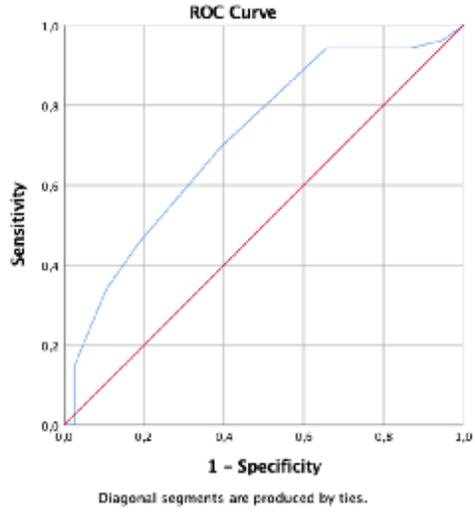

Figure 2. ROC curve of IG% values for GDM diagnosis

Clinical and demographic characteristics of 22 (41%) insulin users with a GDM diagnosis and 31 (59%) non-insulin users were evaluated. There was no statistically significant difference in age, GW, BMI, PLCR, IG%, and HbA1c levels between insulin and non-insulin users. There was no statistically significant difference between the ages of insulin and non-insulin users (33.5±5.2, 32.3±4.9, p=0.373, respectively). Similarly, the weeks of gestation between the two groups did not differ statistically significantly (35.5±3.0 weeks for insulin users, 36.6±2.5 weeks for non-insulin users p=0,144). The mean BMI for insulin and non-insulin users were 31.8±4.4 and 30.4±7.2 (p=0,411), respectively. The PLCR values for insulin users (31.2±6.0) and non-insulin users (32.3±4.5) were also similar (p=0,476). The percentage of immature granulocytes was also similar between insulin and non-insulin users (0.6±0.2, 0.6±0.1, p=0.331, respectively). Lastly, HbA1c levels for insulin and non-insulin users were 5.6±1.0 and 5.3±0.4 (p=0.103), respectively.

The relationship between HbA1c value and IG% value was evaluated in all patients using Pearson's correlation analysis. There was a statistically significant increase in the IG% value with increasing HbA1c value (r: 0.320/ p=0.002). A moderate correlation was found between the HbA1c value and the IG% value.

Similarly, the IG% value was examined using logistic regression analysis to predict the possibility of all patients having GDM. The relationship between the probability obtained from the regression analysis and the IG% value was recorded. The probability of participants having GDM for each IG% value was determined, as shown in Figure 1. Finally, the specificity and sensitivity of the IG% value for GDM diagnosis in pregnant women were evaluated using ROC analysis. In the ROC curve analysis, the area under the curve (AUC) for the IG% value was determined to predict the presence of GDM. The area under the curve (AUC) was measured as 0.713 (0.606-0.821). It was also found that the IG% value could predict the diagnosis of GDM with a sensitivity of 70% and a specificity of 61% at a cut-off value of 0.5 (Figure 2).

Discussion

This study investigated the PLCR and IG% values, which are new inflammatory markers that have not been studied much, in GDM patients. We detected a statistically significant increase in IG% values in GDM patients and for the first time determined a cut-off value for this marker using ROC curve analysis.

The relationship between DM pathogenesis and inflammation is a well-known matter that has been reported many times [3,7,10]. Jindal et al. [10] in their study highlighting the role of inflammation in the pathogenesis of DM detected that MPV, PDW and PLCR values were significantly higher in diabetic patients than in the control group. The role of inflammation has also been demonstrated in GDM patients, as in patients with type 2 diabetes.

Gomez et al. [18] in their review emphasized the similarities between type 2 diabetes and GDM, noting that in many studies, pro-inflammatory cytokines such as TNF-alpha and IL -6 were found to be high and anti-inflammatory cytokines such as IL -10 were found to be low. The same results were also reported by Catalano et al. [19]. In their published review, Khambule

et al. pointed out that GDM risk factors such as age, obesity, and polycystic ovary syndrome are associated with chronic low-grade inflammation, and emphasized the need for new biomarkers [3], as the criteria for diagnosing and monitoring GDM have not yet been finalized. These authors indicated that inflammation-related markers such as adiponectin, TNF-alpha, and IL -6 could be used to diagnose and monitor GDM in early or late pregnancy [3].

In addition to the long-known effects of platelets in thrombus formation, they have also been believed to affect DM and GDM after it was understood that they play a role in the pathogenesis of inflammatory diseases [4]. Many studies have investigated the relationship between platelet parameters such as PCT, MPV, PDW and platelet-to-lymphocyte ratio (PLR) and GDM, with varying results [3,4,17]. Several studies have found an association between MPV and GDM [19,20]. Shahbaz et al. [4] revealed that PCT, MPV, PDW and PLR values among platelet parameters were higher in GDM patients and that PCT values achieved higher sensitivity and specificity than other parameters; however, PLCR and IG% parameters were not investigated in this study. On the other hand, Fashami et al. [22] determined that platelet count, MPV, PCT and PLR values were statistically significantly higher in GDM patients. Other studies have also found a relationship between the MPV value and GDM [23].

Aytan et al. [17], who investigated the PLCR and IG% values, which are the main parameters in our study, established no statistical difference in platelet parameters of GDM patients. These authors referred to publications reporting that platelet markers do not change in GDM patients [24]. In their study, they found that only nucleated red blood cell (NRBC) and red blood cell distribution width (RDW) values were significantly higher [17]. Our study concluded that the PLCR value did not differ significantly between GDM patients and the control group. However, IG% values were statistically significantly different between the GDM and control groups (p=0.002). To the best of our knowledge, the study by Aytan et al. [16] was the first to evaluate the IG% value in GDM patients. This marker has been reported to increase before conventional markers in inflammatory conditions [15]. It goes without saying that the patient group in the study by Aytan et al. mainly included 25-26 weeks of gestation. The authors pointed out that GDM is a subclinical inflammatory state and that IG% is not useful in predicting GDM along with other platelet markers because it is a marker that increases in cases of more significant inflammation [17]. The mean gestational week in GDM patients in our study was 36 weeks. We speculated that the significantly higher IG% value in our study might be due to the fact that the inflammatory state in GDM patients progressed to a level that would affect these markers in later weeks. Accordingly, we hypothesized that IG% values, which Aytan et al. reported to be ineffective in predicting GDM in the early weeks of gestation, could be used in GDM monitoring in later weeks. By analyzing the ROC curve for IG%, we found that the cut-off value of 0.5 was predictive. Our study is the first to determine these values using the ROC curve for IG%, as far as we could detect.

In the present study, we also found that HbA1c values were higher in the GDM group, as expected, and IG% values increased with increasing HbA1c values. This suggests that there is a correlation between the severity of GDM and IG% levels. Insulin is preferred for blood glucose regulation in GDM patients [2]. Since insulin was started in patients with higher blood glucose levels who were thought to have more severe GDM, we investigated whether there was a difference between insulin users and non-insulin users with a GDM diagnosis. No significant difference was detected in age, gestational age, BMI, PLCR, IG%, and HbA1c values between insulin-using and non-insulin-using GDM patients.

Until more precise criteria for diagnosing and monitoring GDM are established, clinicians will continue to search for more effective and clearer criteria to predict and monitor GDM earlier. Inexpensive and routinely examined markers obtained by complete blood count provide valuable information about inflammation. As these markers are used in diagnosis, they may also be valuable in patient monitoring. As information on this topic accumulates, it will guide clinicians.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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